



Australian Government

Department of Health

REDACTED **RATIFIED PICO**

Application 1593

**Bovine bioinductive collagen implant
(REGENETEN™) for the repair of
rotator cuff tear**

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Note: This is an application for listing on the Prostheses List, not a new MBS item. There are currently several clinically-appropriate MBS items that allow Prostheses List Advisory Committee (PLAC)-approved product/device use. If this technology is deemed safe, effective and cost effective for use in the nominated indications, those existing MBS items would be used.

There are two patient subgroups relevant to this application: (1) patients with a partial-thickness rotator cuff tear (PTRCT); and (2) patients with a full-thickness rotator cuff tear (FTRCT).

Table 1:
Summary of PICO criteria for subpopulation 1: Patients with symptomatic partial-thickness cuff tear

Component	Description
Patients	<p>Patients with symptomatic partial-thickness rotator cuff tear (PTRCT):</p> <ul style="list-style-type: none"> that have failed at least 3 months of conservative management (not responded to pain relief^a, modified daily activities and physical therapy); and considered eligible for (or indicated for) surgical repair
Intervention	<p>Arthroscopic surgery with use of bovine bioinductive collagen implant (BCI). <i>Note, standard repair with sutures or anchors is typically not required with use of bovine BCI in this subpopulation (e.g. debridement + bursectomy + bovine BCI)</i></p>
Comparator	<p>Standard arthroscopic surgical repair (without bovine BCI), with repair performed using standard sutures or anchors, using two techniques:</p> <ul style="list-style-type: none"> Take-down repair; OR Trans-tendon repair.
Outcomes	<p>Safety</p> <ul style="list-style-type: none"> Procedural complications Longer-term adverse events Revision surgery <p>Effectiveness</p> <p><i>Functional outcomes</i></p> <ul style="list-style-type: none"> American Shoulder and Elbow Surgeons standardized Form for the Assessment of the Shoulder (ASES) Constant-Murley shoulder score <i>Oxford Shoulder Score (OSS)</i> <i>Shoulder Pain and Disability Index (SPADI)</i> Shoulder pain Post-operative physical therapy Post-operative return to activities Single Assessment Numeric Evaluation (SANE) Progression to full-thickness tear <p><i>Imaging-based outcomes</i></p> <ul style="list-style-type: none"> Tendon thickness Size of the cuff defect (tear size, re-tear rate) <p>Quality of life</p> <ul style="list-style-type: none"> Quality of life measures (e.g. EQ-5D or SF-36)

Component	Description
	<p><i>Healthcare system outcomes</i></p> <p>Cost-effectiveness</p> <ul style="list-style-type: none"> Resource utilisation (surgical, diagnostic tests, follow-up physiotherapy rehabilitation, pain management medication, indirect costs (work days lost)) Cost per life year gained, cost per quality-adjusted life year (QALY) gained, incremental cost-effectiveness ratio (ICER) <p>Total Australian Government healthcare costs</p> <ul style="list-style-type: none"> Total cost to Medicare Benefits Schedule and Australian Government budgets.

Abbreviations: EQ-5D = EuroQol-5 dimension scale; SF-36 = Short Form 36 health survey

^a Including nonsteroidal anti-inflammatory drugs (NSAIDs) ± corticosteroid injections

Table 2:

Summary of PICO criteria for subpopulation 2: Patients with symptomatic full thickness rotator cuff tear

Component	Description
Patients	<p>Patients with symptomatic full-thickness rotator cuff tear (FTRCT) :</p> <ul style="list-style-type: none"> that have failed at least 3 months of conservative management (not responded to pain relief^a, modified daily activities and physical therapy); and considered eligible for (or indicated for) surgical repair
Intervention	<p>Arthroscopic or 'mini-open', standard surgical repair with use of bovine BCI^b.</p> <p><i>Note, standard repair with sutures or anchors are required with use of bovine BCI in this subpopulation (e.g. debridement + bursectomy + surgical repair + bovine BCI).</i></p>
Comparator	<p>Standard surgical repair (without bovine BCI), with repair performed using standard sutures or anchors, performed arthroscopically or with 'mini-open' approach</p>
Outcomes	<p>Safety</p> <ul style="list-style-type: none"> Procedural complications Longer-term adverse events Revision surgery <p>Effectiveness</p> <p><i>Functional outcomes</i></p> <ul style="list-style-type: none"> American Shoulder and Elbow Surgeons standardized Form for the Assessment of the Shoulder (ASES) Constant-Murley shoulder score <i>Oxford Shoulder Score (OSS)</i> <i>Shoulder Pain and Disability Index (SPADI)</i> Shoulder pain Post-operative physical therapy Post-operative return to activities Single Assessment Numeric Evaluation (SANE) <p><i>Imaging-based outcomes</i></p> <ul style="list-style-type: none"> Tendon thickness Size of the cuff defect (tear size) <p>Quality of life</p> <ul style="list-style-type: none"> Quality of life measures (e.g. EQ-5D or SF-36)

Component	Description
	<p><i>Healthcare system outcomes</i></p> <p>Cost-effectiveness</p> <ul style="list-style-type: none"> Resource utilisation (surgical, diagnostic tests, follow-up physiotherapy rehabilitation, pain management medication, indirect costs (work days lost)) Cost per life year gained, cost per quality-adjusted life year (QALY) gained, incremental cost-effectiveness ratio <p>Total Australian Government healthcare costs</p> <ul style="list-style-type: none"> Total cost to Medicare Benefits Schedule and Australian Government budgets.

Abbreviations: EQ-5D = EuroQol-5 dimension scale; SF-36 = Short Form 36 health survey

^a Including nonsteroidal anti-inflammatory drugs ± corticosteroid injections

^b The primary reason for use of REGENETEN is to repair rotator cuff tears in appropriate patients. The proposed TGA indication is REGENETEN Bioinductive Implant for the management and protection of rotator cuff tendon injuries in which there has been no substantial loss of tendon tissue. The applicant agreed to incorporate wording from the proposed TGA indication into the eligible population description (i.e. rotator cuff tears where there has been no substantial loss of tendon tissue).

[PICO or PPICO rationale for therapeutic and investigative medical services only](#)

Population

The population that relates to the Prostheses List request are patients who receive a bovine bioinductive collagen implant (BCI) (REGENETEN™), used with surgical repair, who have symptomatic rotator cuff tears of the shoulder. Specifically, there are two subpopulations which can be grouped by depth of the rotator cuff tear:

- Subpopulation 1: Patients with symptomatic **partial-thickness** rotator cuff tear (PTRCT) who have failed at least three months of conservative (non-surgical) management; and
- Subpopulation 2: Patients with symptomatic **full-thickness** rotator cuff tear (FTRCT) who have failed at least three months of conservative (non-surgical) management.

The distinction of these two patient subgroups is important, given current approaches to surgical management differ, based on if the tear is partial or full-thickness (and among other variables).

In addition, the Applicant proposed that, in order to access this treatment, patients should not have responded to conservative (i.e. non-surgical) management, including pain relief (e.g. nonsteroidal anti-inflammatory medication (NSAIDs) ± corticosteroid injections), modified daily activities and physical therapy (e.g. physiotherapy). *This was similar to the definition applied in the early feasibility Australian studies by Bokor et al. (1, 2).*

The clinical work-up includes documenting patient history and symptoms (mobility, stability, pain, strength) patient characteristics (particularly age, smoking, social and occupational context), and establishing the morphological features of the tear by physical examination and medical imaging (3).

The Applicant indicated that REGENETEN™ is not intended to be used in acute trauma.

Background

The rotator cuff provides glenohumeral joint stability (3). It is a group of four muscles and their tendons (supraspinatus, infraspinatus, teres minor, and subscapularis) at the shoulder joint which form a multilayered horseshoe shape cuff around the head of the humerus bone (4). Each tendon has a separate footprint with a wide range of widths and lengths (range medial to lateral: 12-33mm; range anterior to posterior: 15-55mm; Table 11 in Appendix) (5).

Rotator cuff injury can range from simple inflammation to tears of the muscles or tendons. Rotator cuff tears may result due to a degeneration of the tendon quality or due to trauma, where a tear arises from a major injury to otherwise healthy tissue. Most tears are degenerative tears and are due to the progression of chronic tendonitis¹, which may or may not be symptomatic (3). However, rotator cuff tears usually occur as a result of trauma, and are rare in the young (age < 35 years) (6). Several risk factors have been identified in predisposing individuals to the development of rotator cuff tears; increasing patient age, smoking, hypercholesterolemia, and family history. The Applicant stated that each of these may play an additive role to the underlying influence of age-related degeneration in the development of rotator cuff disease.

Subpopulation 1

PTRCTs do not extend through the full-thickness of the tendon. They can involve any of the four rotator cuff tendons and are typically classified by location: articular sided, bursal side, or intratendinous (which are only seen on imaging) (7). Subclassification includes the size (or depth) of the tear, which can be represented as percentage of the tendon thickness torn. The Ellman classification system (8) classifies PTRCTs by determining the amount of exposed articular footprint. Specifically, Grade I (*low*): < 3mm (<25% tendon thickness); Grade II (*medium*): 3-6mm (25-50% tendon thickness); and Grade III (*high*): >6mm (>50% tendon thickness, but not full-thickness); Table 12 in Appendix) (5, 7). While widely accepted, this classification system does not take into account a number of factors including: an analysis of tissue quality, the area of tearing (i.e., not just thickness but anterior to posterior and medial to lateral), or the aetiology of the tear itself (5). In addition, controversy exists around the amount of footprint needed for a tear to be classified as a 50% partial-thickness tear (7).

The current Australian evidence base (Bokor et al (1, 2)) for bovine BCI in subpopulation 1 is in patients with symptomatic ≥ Grade II (>25% tendon thickness) PTRCTs (see Table 4 below). PASC noted that patients with grade 1 PTRCTs would not be eligible for REGENETEN, as they are usually asymptomatic.

The Applicant stated that the literature demonstrates that articular-sided tears, which can be subclassified as partial articular-sided rotator cuff tears (PASTA), are at least twice as common as bursal-sided tears, and that most tears involve the supraspinatus tendon (9).

The current Australian evidence base (Bokor et al (1, 2)) for the proposed intervention is exclusively in supraspinatus tears (PTRCT and FTRCT; see Table 4 below). Partial-thickness tears are 2-3 times more likely, and often much more painful, than full-thickness tears (10), where the tendon is no longer connected to the bone.

¹ Note 'tendinitis' implies a pathology that is not strictly correct. Instead, one should use tendinosis, which is not an inflammatory disorder. Tendinosis (tendinitis) is caused by collagen fibre fatigue and usually develops from repetitive activity at, or above, shoulder height (NZGG 2004; 6)

Spontaneous healing of untreated rotator cuff tears is rare (11-13), and without intervention, a partial-thickness tear is likely to enlarge and propagate into full-thickness tears (14, 15). Progression of symptomatic partial-thickness tears to full-thickness tears with non-operative treatment has been seen in 18% of patients followed up for over 1 year, with a further 34% exhibiting increase in partial tear size (16). Because increased tear size and poorer muscle quality are associated with poorer healing after surgical repair, repair before progression may improve outcomes (13). The risk of tear progression has been shown to correlate with percentage tendon thickness at presentation with progression observed in 55% of patients with $\geq 50\%$ tearing of tendon thickness at presentation compared to 14% tear progression in those who had $< 50\%$ tearing (17).

Subpopulation 2

FTRCTs involve the full detachment of the tendon that attaches the muscles from the shoulder blade to the head of the humerus. They can be classified by the DeOrto and Cofield classification system (18), which classifies FTRCTs as either small ($< 1\text{cm}$), medium (1-3cm), large (3-5cm) and massive ($>5\text{cm}$)². However, some prefer to classify a massive tear as involving two or more tendons; usually the supraspinatus and infraspinatus, but also supraspinatus and subscapularis (6).

The current Australian evidence base (Bokor et al (1, 2)) for bovine BCI in subpopulation 2 is in patients with symptomatic [chronic shoulder pain $\geq 3\text{months}$] medium (1-3cm) FTRCTs. However, it was noted in a recent US study (Thon et al 2019 (19)) that bovine BCI was applied to a population with more advanced disease severity: patients with symptomatic large and massive ($>3\text{cm}$ and minimum 2-tendon involvement) FTRCTs (see Table 4 below).

PASC queried the 3-month wait for the FTRCT population, as it would seem unlikely this population would wait 3 months before a surgical procedure. PASC confirmed this would be rare, but accepted the population 2 description should remain as is.

Prevalence and/or incidence of population

The prevalence of rotator cuff tear increases with age; rotator cuff tears are present in approximately 25% of individuals in their 60s and 50% of individuals in their 80s (13).

The incidence of cuff tears ranges from 5 to 40% (20, 21); however, not all rotator cuff tears are symptomatic, so the true incidence is difficult to determine. Approximately one third of silent rotator cuff tears will become symptomatic (22).

Utilisation estimates

The Applicant initially presented a market share approach using the four nominated MBS items for 'standard surgical repair' of the rotator cuff (Items 48960, 48906, 48909, and 48918; refer to Table 7 for further detail on MBS item descriptors). In 2017-18 financial year, there were 17,632 services for these items, and the Applicant noted utilisation was similar with previous four years (i.e. little to no growth in utilisation). However, MBS items 48960 and 48918 also include shoulder reconstruction, resection and replacement services, and using this approach would likely misrepresent (overestimate) the eligible population for bovine BCI in rotator cuff surgical repair.

Thus, the Applicant presented an epidemiological approach estimating the expected utilisation of bovine BCI in rotator cuff surgical repair in Australia over the next four years. Specifically, they

² Measured by the length of the greatest diameter of the tear

applied the incidence of 131 per 100,000 rotator cuff repairs from a population-based study in Finland (23) to the current adult Australian population estimates from the Australian Bureau of Statistics (ABS) (3222.0 Series B (24)). The Applicant then derived the proportion of procedures that would be performed in the private setting **REDACTED**. However, it was noted the Applicant's uptake rates were based on assumption, and not evidence, and could be considered low if comparative effectiveness of bovine BCI in rotator cuff surgical repair is established during the assessment phase (Table 3).

Table 3: Estimated utilisation of bovine BCI in rotator cuff surgical repair over the next five years

-	Parameter	Method/Source	Year 1	Year 2	Year 3	Year 4
			2020	2021	2022	2023
A	Total Australia population	ABS	25,873,480	26,301,274	26,727,025	27,147,199
B	Aged ≥18 years	ABS	20,100,838	20,429,953	20,757,917	21,082,471
C	Incidence of rotator cuff repair (per 100,000)	Paloneva 2015 (23)	131	131	131	131
D	Estimated incident population	B x C	26,332	26,763	27,193	27,618
E	% procedures performed in private setting	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
F	Total rotator cuff repairs in private setting	D x E	11,849	12,043	12,237	12,428
G	Uptake of bovine BCI surgery	Assumption	REDACTED	REDACTED	REDACTED	REDACTED
H	Estimated utilisation of bovine BCI	F x G	REDACTED	REDACTED	REDACTED	REDACTED

Source: Table 3, p18 of Application Form

Abbreviations: ABS = Australian Bureau of Statistics; APRA = Australia Prudential Regulation Authority; BCI = bioinductive collagen implant

The Applicant stated there are no apparent constraints in the health care system that would impact on uptake.

Regarding risk of leakage, the Applicant expected this to be low, given the following:

- The proposed indication includes both PTRCTs and FTRCTs, both of which are objectively diagnosed using magnetic resonance imaging (MRI). However, it is noted in the I.S.Mu.L.T (Italian Society of Muscles, Tendons and Ligaments *Rotator Cuff Tear Guidelines*³ that, while diagnostic accuracy of MRI for detection of FTRCTs is excellent, it is more limited for PTRCTs (26); and
- It is unlikely that patients without symptoms would elect to undergo surgery.

Rationale

The description of patient populations included in the current peer-reviewed studies (and upcoming studies) for bovine BCI in rotator cuff surgical repair is summarised in Table 4.

Table 4: Description of patient populations for bovine BCI in rotator cuff surgical repair

Study ID	Indication	N	Study type	Selected patient criteria	Country
PEER REVIEW					
Subpopulation 1 (PTRCT)					
ACTRN12611001082998 Bokor et al. (2016) (2)	Supraspinatus tendon <u>Grade</u> Int: 6 (46%)	13	Prospective, OL, NR, single arm, SC.	<ul style="list-style-type: none"> • Patients aged 40-66 years at surgery • Chronic shoulder pain > 3 months (resistant to analgesics, anti-inflammatory medication, and physical therapy) 	Australia

³ Includes the Australian 2013 "Clinical practice guidelines for the management of rotator cuff syndrome in the workplace - Technical Report"

Study ID	Indication	N	Study type	Selected patient criteria	Country
	High: 7 (54%)		Level IV ^a	<ul style="list-style-type: none"> Exclusion criteria: patients with shoulder instability; grade 3 ≥ chondromalacia; or grade 2 ≥ fatty infiltration of supraspinatus. Recent steroid use, insulin-dependent diabetes, heavy smoking, genetic collagen disease, chronic inflammatory disease, and index shoulder with previous cuff surgery. Contraindications: hypersensitivity to collagen 	
Schlegel et al. 2018 (27)	Supraspinatus tendon <u>Grade</u> Int.: 12 (36%) High: 21 (64%)	33	Prospective, OL, NR, single arm, MC. Level IV ^a	<ul style="list-style-type: none"> Patients aged ≥ 21 years Chronic, degenerative, PTRCT involving at least 25% of tendon thickness (Grade II-III) unresponsive to conservative management (pain medication, physical therapy or injections) Exclusion criteria: patients with FTRCT, PTRCT caused by acute injury. Patients with shoulder instability; grade 3 ≥ chondromalacia; or grade 2 ≥ fatty infiltration of supraspinatus, severe calcification within index shoulder. Recent steroid use, insulin-dependent diabetes, heavy smoking, genetic collagen disease, chronic inflammatory disease, and index shoulder with previous cuff surgery. 	US
Subpopulation 2 (FTRCT)					
Thon et al. 2019 (19)	<ul style="list-style-type: none"> Large (2-tendon): 11 (48%) Massive (3-tendon): 12 (52%) Revision surgery 16 (70%) 	23	Prospective, OL, NR, single arm, MC. Level IV ^a	<ul style="list-style-type: none"> Patients aged ≥ 30 years Large or massive rotator cuff tear > 3cm and retraction of at least 3cm measured on preoperative MRI Exclusion criteria: Patients aged < 30 years; extensive prior treatment incl. physical therapy, injections AND/OR anti-inflammatory medication for >6 weeks before surgery; Hamda grade ≥ 3 preoperative rotator cuff arthropathy; Goutallier grade ≥ 3 muscle atrophy, <2-year clinical follow-up and unwilling to complete study protocol 	US
Subpopulations 1 & 2 (mixed)					
ACTRN12611001 082998 Bokor et al. (2015) (1)	<u>FTRCT</u> : 8 (89%) <ul style="list-style-type: none"> Medium (1-3cm) <u>PTRCT</u> : 1 (11%) <ul style="list-style-type: none"> High grade (10mm), bursal sided. All supraspinatus tendon.	9	Prospective, OL, NR, single arm, SC. Level IV ^a	<ul style="list-style-type: none"> Patients aged 40-66 years at surgery Chronic shoulder pain > 3 months (resistant to analgesics, anti-inflammatory medication, and physical therapy) Exclusion criteria: patients with shoulder instability; grade 3 ≥ chondromalacia; or grade 2 ≥ fatty infiltration of supraspinatus. Recent steroid use, insulin-dependent diabetes, heavy smoking, genetic collagen disease, chronic inflammatory disease, and index shoulder with previous cuff surgery. Contraindications: hypersensitivity to collagen	Australia
Arnoczky et al. 2017 (28)	Supraspinatus tendon <u>FTRCT</u> : 5 (71%) <ul style="list-style-type: none"> Medium: 3 Large: 1 Massive: 1 Revision surgery: 1 <u>PTRCT</u> : 2 (29%) <ul style="list-style-type: none"> High grade: 1 	7	Retro, OL, NR, single arm, SC. Level IV ^a	<ul style="list-style-type: none"> Patients who underwent rotator cuff repair with collagen implant No Exclusion criteria 	US
YET TO BE COMPLETED					
Subpopulation 1 (PTRCT)					

Study ID	Indication	N	Study type	Selected patient criteria	Country
REGEN PUB 2018 REDACTED	High grade (>50%)	118	Prospective, OL, NR, parallel assignment ^b , MC. Level IV ^a	<ul style="list-style-type: none"> • Male of female ≥ 18 years (understand English) • High grade (50% tendon thickness) PTRCT • Failed conservative management, defined as 4-6 weeks of physical therapy, activity modification, and shoulder injection • Exclusion criteria: prior surgery on index shoulder within 12 months, failed primary rotator cuff surgery, grade 3 ≥ fatty infiltration of index shoulder, recent steroid use, insulin-dependent diabetes, heavy smoking, , chronic pain disorders. metastatic disease, concomitant surgeries for bone defects, concomitant biceps tendinosis, RA, advanced OA, hypersensitive to bovine-derived materials 	US
Subpopulations 1 & 2 (mixed)					
Registry REDACTED	PTRCT or FTCRT	483 ^c	Observational registry study, MC. Level IV ^a	<ul style="list-style-type: none"> • Patients aged ≥ 21 years (understand English) • Exclusion criteria: hypersensitive to bovine-derived materials 	US
Post-market evaluation REDACTED	PTRCT or FTCRT supraspinatus	148	Prospective, OL, NR, parallel assignment, MC. Level IV ^a	<ul style="list-style-type: none"> • Patients aged ≥ 21 years (understand English) • Medium or large PTRCT OR very small FTCRT • Chronic shoulder pain > 3 months unresponsive to conservative therapy (pain medication, physical therapy and injections) • MRI of shoulder within 60 days • Willing to comply with post-operative rehabilitation • Exclusion criteria: massive rotator cuff tears (≥5cm), acute rotator cuff tears, previous rotator cuff surgery, patients with shoulder instability; grade 3 ≥ chondromalacia; or grade 2 ≥ fatty infiltration of supraspinatus. Recent steroid use, insulin-dependent diabetes, heavy smoking, genetic collagen disease, history of autoimmune disorders, chronic inflammatory disease, and index shoulder with previous cuff surgery. Contraindications: hypersensitivity to bovine-derived materials 	US

Source: Compiled from Application Form and accessing Clinicaltrials.gov

Abbreviations: FTRCT = full-thickness rotator cuff tear; MC = multi-centre; NR = non randomised; OA = osteoarthritis; OL = open label; PTRCT = partial-thickness rotator cuff tear; Retro = retrospective; RA = rheumatoid arthritis; SC = single-centre; US = United States; int = intermediate;

^a National Health and Medical Research Council (NHMRC) levels of evidence

^b Includes comparator arm with surgical treatment of partial-thickness rotator cuff tears using standard techniques

^c Listed as enrolled on Clinicaltrials.gov

The Australian studies by Bokor et al. (1, 2) restricted use of bovine BCI in rotator cuff surgical repair to patients aged 40-66 years (at date of surgery). *The reason for the age criteria was unclear.* However, it was noted in the I.S.Mu.L.T 'Rotator Cuff Tear Guidelines' that "there is no 'cut-off' age for the surgery indication, which must be evaluated from patients' activities and differences between chronological and physiological age" (Level of recommendation D⁴(26)).

Key trial exclusion criteria for Bokor et al. (1, 2) were (*noting these do not apply to the Applicant's two proposed subpopulations*):

⁴ Indications from experts ("there is no evidence")

- patients with shoulder instability, OR grade 3 \geq chondromalacia; OR grade 2 \geq fatty infiltration of supraspinatus;
- patients with existing co-morbid conditions, including insulin dependent diabetes, heavy smoking, genetic collagen disease, and chronic inflammatory disease; and
- patients who had received previous rotator cuff surgery of the index (affected) shoulder.

Feedback from the Applicant (32) indicates the Bokor et al. studies (1, 2) were very early feasibility studies on the product and, as such, more restrictive criteria were used. The Applicant therefore claims the Bokor et al. study population does not represent those symptomatic patients with a painful shoulder (with proven cuff disease) and not responsive to 3 months of conservative, non-surgical management (who are most likely to gain benefit from the use of REGENTEN™ in the repair of rotator cuff disease).

Schlegel et al. 2018 (27), the largest US-based study for bovine BCI in rotator cuff surgical repair had broadly similar patient eligibility criteria to Australian studies by Bokor et al. (1, 2), although differences were noted with age criteria (> 21 years), excluding patients with PTRCTs caused by acute injury and excluding patients with severe calcification of index shoulder.

A more recent US study by Thon et al. (2019) recruited patients with more advanced FTRCTs: large and massive tears, and the majority of the population (70%) had received previous primary rotator cuff repair and now were undergoing revision surgery with use of bovine BCI.

It was noted the upcoming Registry had very limited eligibility criteria, indicating that bovine BCI could be used in the full spectrum of patients treated with rotator cuff tears (i.e. not excluding patient co-morbid conditions). However, the upcoming pivotal REGEN PUB 2018 will exclude patients with arthropathy conditions of the shoulder, such as osteoarthritis and rheumatoid arthritis, in patients with symptomatic PTRCTs.

Current management of intended population

Typically, patients with rotator cuff tears present to their general practitioner with shoulder instability, pain and/or weakness and decreasing shoulder power and function (15). Rotator cuff tears most frequently occur with general wear and tear, and most people don't remember injuring their shoulder. These "degenerative tears", if not associated with arm weakness, may be successfully treated without surgery. Medical treatment is always the first management option of degenerative tears of rotator cuff tendons (3), and can involve avoiding overhead activities, regular simple pain relief (e.g. NSAIDs) and gentle physiotherapy. In more severe cases, increased pain relief using corticosteroid injections, may be used (26). If a rotator cuff tear is suspected, early referral to a physiotherapist may be appropriate (33). Referral for imaging (i.e. X-ray AND/OR ultrasound AND/OR MRI) may also be warranted where there is evidence or suspected serious damage/disease (6, 34). The Applicant stated that MRI is typically used in most cases to diagnose PTRCTs and FTRCTs. *All patients in Bokor et al (1, 2) had preoperative MRI scans.*

When symptoms fail to improve following a minimum of 3 months of conservative treatment, or where a tear has occurred from sudden trauma or acute injury and is impacting on comfort and function, referral to an orthopaedic surgeon for further review and possible surgical repair of the tear is indicated (33). The decision to perform surgical repair is dependent on clinical and morphological factors, and patient characteristics, patient eligibility and preference (3). Specifically, the orthopaedic surgeon will determine treatment strategies for the rotator cuff repair primarily

based on the location, anatomy and the size of the defect, with 'surgery timing', functionality, age and gender as important secondary considerations (26).

Failure of anatomic repairs is reportedly 20-40% after primary rotator cuff repairs and is even higher in revision cases. Re-tear of a rotator cuff repair has been associated with a multitude of factors including patient age, tear dimensions, and tendon tissue quality (35). A recent study found that re-tears following rotator cuff repair primarily occurred between 6-26 weeks, with a substantial number of re-tears occurring between 12-26 weeks (36). With over one-quarter of repairs failing to achieve durable integrity (i.e. re-tears) of the rotator cuff at two years (37), the inability to obtain high healing rates has spurred the investigation of biological options to augment rotator cuff repairs (19) (e.g. application of bovine BCI in surgical repair of rotator cuff tears).

If left untreated, shoulder problems and pain can lead to significant disability, limitations in activity and restrict participation in major life areas such as work and employment, education, community, social and civic life.

However, some patients may not be eligible for surgery or may have a preference to not have surgery. In this instance, conservative management is continued.

For further detail on the management options for the proposed populations, refer to the 'Current and proposed clinical management algorithm' (Figure 3).

Intervention

The proposed intervention is the use of bovine BCI (REGENETEN™) in addition to:

- arthroscopic surgery (e.g. debridement and bursectomy, without standard surgical repair) in **subpopulation 1**; and
- arthroscopic or 'mini- open' standard surgical repair (e.g. debridement and bursectomy, plus standard surgical repair with sutures or anchors) in **subpopulation 2**.

Feedback from the Applicant (32), indicated that REGENETEN™ is not used as an adjunct to surgical repair of the rotator cuff. Its use is central in this procedure in both subpopulations.

The Applicant stated that bovine BCI is designed to induce the formation of new tendon-like tissue that will biologically augment the degenerated rotator cuff tendon. The Applicant claimed the physical and chemical properties of the scaffold provide a layer of collagen between a flat tendon and the surrounding tissue, permitting collagen in-growth into the scaffold and promoting collagen re-modelling, with alignment of the collagen fibres in the direction of stress in the tendon (i.e. promote tendon vascularisation and growth).

Procedure

The procedure is performed under general anaesthetic (2) in the hospital inpatient setting (private and public), with overnight hospitalisation. The procedure can be performed arthroscopically (minimally invasive keyhole surgery) or as mini-open surgery (which involves a small incision typically 3 to 5 cm long). The Applicant stated that arthroscopic and mini-open repair surgical techniques are associated with similar outcomes, with both being able to be used interchangeably, depending on patient and rotator tear characteristics (38, 39). This is similar to recommendations in the *I.S.Mu.L.T 'Rotator Cuff Tear Guidelines'* which state there are no statistically significant differences between the two techniques, in terms of relapse, complications and functional outcomes (26).

The Applicant advised, based on expert opinion, that the average duration of surgery (i.e. with use of REGENETEN) is 15-30 minutes, for either partial-thickness or full-thickness repairs [Application Form, p20]. However, for **subpopulation 1**, this is performed in phase three of the surgical repair procedure (as standard surgical repair with sutures or anchors is not required in this population); and for **subpopulation 2**, this is performed in phase four of the surgical repair procedure (as surgical repair with sutures or anchors is required in addition to bovine BCI). *If surgical repair is performed, this is immediately prior to applying bovine BCI (1, 19).* The Applicant's summary of the phases required for surgery in each subpopulation is provided in Table 5 below.

Table 5: Description of surgical procedures with use of bovine BCI in both populations

-	Subpopulation 1	Procedure time	Subpopulation 2	Procedure time
Phase 1	Anaesthesia and skin penetration	-	Anaesthesia and skin penetration	-
Phase 2	Debridement, diagnosis and bursectomy	-	Debridement, diagnosis and bursectomy	-
Phase 3	Arthroscopic surgical repair with REGENETEN	15-30 minutes	Standard arthroscopic or mini-open surgical repair (Sutures or anchors) ^a	30-60 minutes ^a
Phase 4	N/A	N/A	Arthroscopic surgical repair with REGENETEN	15-30 minutes

Source: Applicant feedback

N/A = not applicable

^a As per comparator; refer to comparator section for description of these surgical procedures

The Applicant stated that, for both subpopulations, the proposed intervention is intended to be performed once.

The procedure is performed by orthopaedic surgeons. *The Applicant and its nominated clinical expert confirmed at PASC that no additional training is required by orthopaedic surgeons to use REGENETEN in appropriate patients. However, this should be verified during the assessment phase.*

The Applicant also provided the detailed surgical steps in arthroscopic use of REGENETEN™ (as published in Wasburn et al. 2017 (14) (see below) and provided this schematically in Figure 1.

1. Diagnostic arthroscopy is performed.
2. Tendon markers along the anterior edge of the supraspinatus are placed in a percutaneous fashion.
3. Entry is made into the subacromial space, and bursectomy is performed through a standard lateral portal.
4. A 5-mm guidewire is placed at the lateral edge of the rotator cuff footprint.
5. The graft is hydrated (in saline) for one minute
6. The graft is loaded into the delivery instrument.
7. The graft is introduced until the red button becomes prominent.
8. The graft is deployed.
9. A second lateral cannula is placed just off the lateral edge of the acromion.
10. Soft-tissue staples are placed through the graft into the underlying rotator cuff.
11. The tendon markers are removed.
12. A bone stapler awl is used to tension the graft from the lateral portal.
13. The bone staples are placed.
14. The instruments are removed, and the wounds are closed [Application Form, p12]

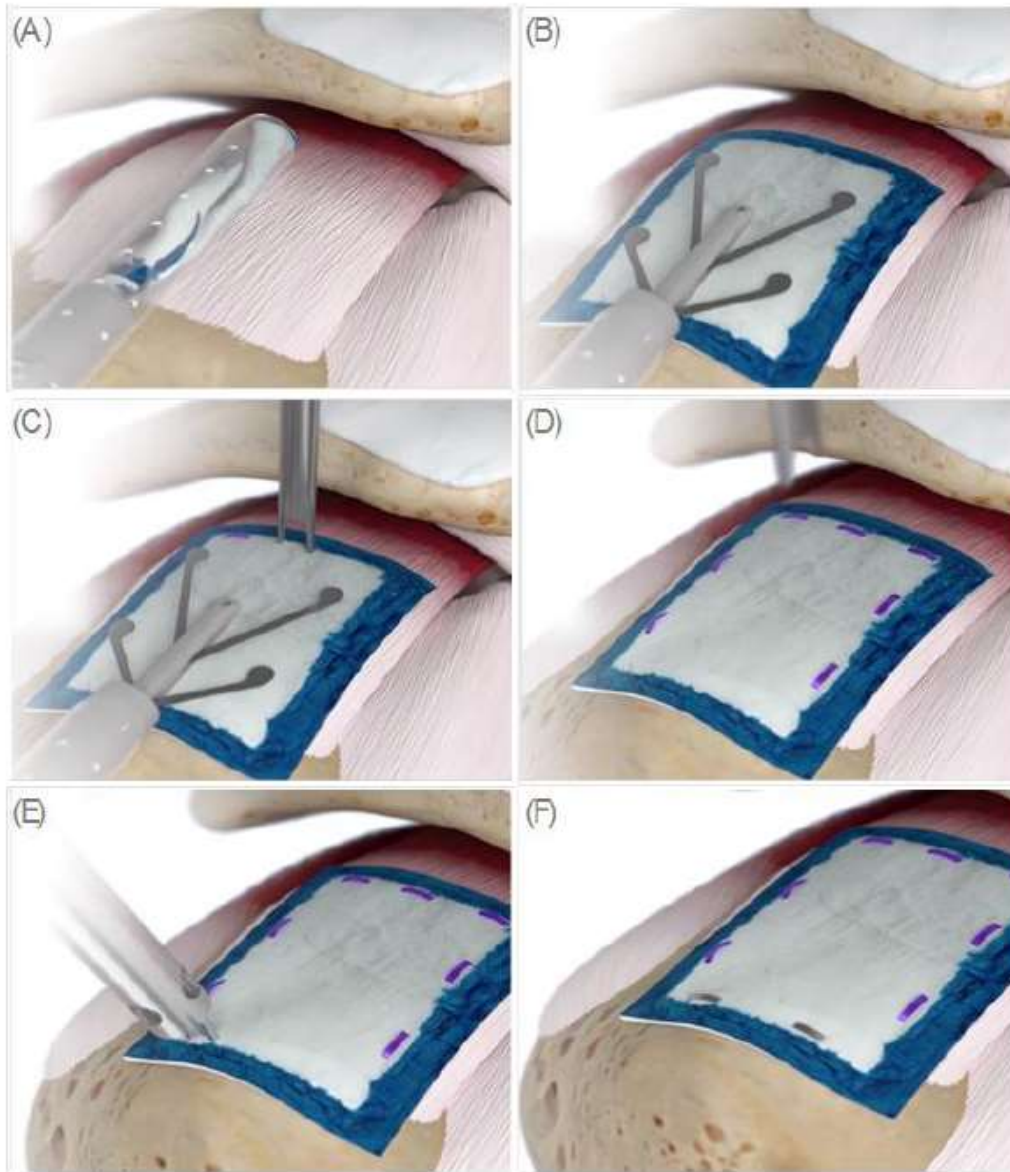


Figure 1: Application of bovine BCI (using REGENTEN™)

Source: Applicant feedback (32)

Legend: A. Bioinductive Implant Placement Cannula insertion; B. Bioinductive Implant Placement deployment; C. Tendon Anchor insertion at medial edge; D. Completed Tendon Anchor insertion at posterior and anterior edges; E. Bone Anchor insertion at lateral edge; F. Fully fixated REGENTEN Bioinductive implant

Note, the equipment required includes standard arthroscopic equipment, the Bovine Bioinductive Patch System (**REDACTED**) and an 8-mm cannula (14). The Applicant stated that single use consumables included: three clear cannulas, and disposable instrument set comprising: two clear lateral cannulas, guide wire, graft delivery system, metal staple delivery instrument, and bone stapler.

Post-operative care

Following the procedure (performed arthroscopically or ‘mini-open’ approach), standard pain management measures should be undertaken. The Applicant stated that the postoperative protocol

is immediate range of motion as tolerated, with the patient using a sling for comfort. Strengthening can begin once full range of motion has returned.

Specifically, post-operative care in Bokor et al. for patients:

- with symptomatic PTRCTs (**subpopulation 1**) was: discontinuation of the sling when comfortable (maximum of 1 week); progress from passive-assisted to active motion (under physiotherapy supervision), with no restrictions on arm for 6 weeks (2); and
- with symptomatic FTRCTs (**subpopulation 2**) a more extensive rehabilitation program was followed: discontinuation of sling during first six weeks; passive-assisted motion for six weeks and progression to active motion beyond six weeks; and after 12 weeks, a gradual resistance program was adopted (1).

Access

The Applicant stated there are no current limitations on provision of the proposed medical service, with respect to accessibility.

Prosthesis

The bovine BCI is made from highly purified type I bovine collagen and engineered into a highly orientated, highly porous (85-90% porosity) scaffold that once is hydrated was approximately 2mm thick (27). The prosthesis is not designed to provide structural support immediately after surgery and absorbs within six months (27). It is attached under a slight amount of tension to assure good contact with the underlying tendon (1). The staples attaching the bovine BCI to the tendon (polylactic acid (PLA) staples, attached anteriorly, posteriorly and medially) and bone (polyether ether ketone (PEEK) staples, attached laterally) are designed to absorb within approximately 12 months (1, 2). REDACTED. In Bokor et al. (1, 2) the implant size was selected to cover almost the entire width of the repaired supraspinatus tendon in repairs of patients with symptomatic PTRCT (**subpopulation 1**) or symptomatic FTRCT (**subpopulation 2**).

Regulatory information

The medical device (bovine BCI) is classified as a Class III medical device as per the TGA. Bovine BCI is not currently listed on the Australian Register of Therapeutic Goods (ARTG); however, it is in the process of being considered by the TGA for inclusion:

Application number and date of submission: REDACTED

Estimated date by which TGA approval can be expected: REDACTED

TGA approved indication(s) and approved purpose(s), if applicable: The REGENETEN™ Bioinductive Implant is indicated for the management and protection of rotator cuff tendon injuries in which there has been no substantial loss of tendon tissue [Application Form, p5]

It was noted the proposed TGA indication for REGENETEN™ includes a requirement that the rotator cuff tendon has no substantial loss of tendon tissue.

PASC queried the proposed TGA indication, which states that REGENETEN must only be used “when there is no substantial loss of tissue”. The Applicant clarified that this refers to the amount of viable tissue left at the injured site, which there must be a reasonable amount of before the device is effective. PASC recommended that the population description mirror the TGA indication as closely as possible. The Applicant agreed to incorporate wording from the proposed TGA indication into the

eligible MSAC population description (i.e. rotator cuff tears where there has been no substantial loss of tendon tissue).

REDACTED

Rationale

The description of the proposed intervention (as provided in the included peer-reviewed studies) is summarised in Table 6. It was noted for all studies that the same bovine BCI prosthesis was used (REDACTED), and in the majority of uses, surgery was performed arthroscopically. *However, there was some variation in the surgical procedures that bovine BCI was used with (e.g. ± surgical repair and/or ± biceps tenodesis or tenotomy). The reason for these differences with use of bovine BCI may be due to evolution of the technology over time, differences in patient populations (PTRCTs vs. FTRCTs), surgeon experiences, and different institutional practices.*

Subpopulation 1

Bovine BCI was applied without performing a repair (i.e. non-repair surgery; subacromial decompression/bursectomy, as listed in phases 1-3 above) in all Australian patients in Bokor et al. 2016 (2), as well as the more recent multi-centre US study by Schlegel et al. 2018 (27). However, it was noted that one patient with high-grade, bursal-sided PTRCT, received conversion to full thickness lesion at surgery (i.e. take-down repair), prior to application of bovine BCI, in the earlier Australian trial by Bokor et al. 2015 (1).

PASC requested clarification around the procedure for patients with symptomatic PTRCTs. In the early published Australian study, one patient with a high grade PTRCT [Bokor et al. 2015] was treated with take-down repair and REGENETEN, whereas in the subsequent Australian study [Bokor et al. 2016], all patients with PTRCTs were treated with debridement and bursectomy and REGENETEN (i.e. not in conjunction with standard surgical repair with take-down or trans-tendon repair).

Thus, PASC queried whether take-down repair is replaced with REGENETEN for all PTRCTs. The Applicant clarified that REGENETEN replaces take-down repair when using REGENETEN.

Subpopulation 2

Bovine BCI was applied with performing a repair in all patients with symptomatic FTRCTs in Bokor et al. 2015 (89% study population) (1) and all patients in Thon et al. 2019 (19). Surgical repair was predominantly performed with double-row suturing methods in this subpopulation (see Table 6).

PASC noted that, for FTRCTs, standard surgical repair and REGENETEN are both required.

Table 6: Description of surgical techniques for bovine BCI included in current peer reviewed evidence

Study ID	N	Pre-intervention surgical procedures (i.e. prior to application of bovine BCI)	Intervention surgical procedure (i.e. application of bovine BCI)	Country
Subpopulation 1 (PTRCT)				
ACTRN12611001 082998 Bokor et al. (2016) (2)	13	<ul style="list-style-type: none"> • Arthroscopic assessment^a • Subacromial bursectomy and decompression 	<ul style="list-style-type: none"> • Bovine BCI attached to bursal side of tendon^b without standard surgical repair <ul style="list-style-type: none"> • Arthroscopic: 13 (100%) • Mini-open conversion: 1 	Australia
Schlegel et al. 2018 (27)	33	<ul style="list-style-type: none"> • Arthroscopic assessment^c • Subacromial bursectomy and decompression 	<ul style="list-style-type: none"> • Bovine BCI attached to bursal side of tendon^b without standard surgical repair <ul style="list-style-type: none"> • Arthroscopic: All patients 	US

Study ID	N	Pre-intervention surgical procedures (i.e. prior to application of bovine BCI)	Intervention surgical procedure (i.e. application of bovine BCI)	Country
Subpopulation 2 (FTRCT)				
Thon et al. 2019 (19)	23	<ul style="list-style-type: none"> • Arthroscopic assessment and extensive debridement^c • Subacromial bursectomy and decompression • Capsular release (360°) • Arthroscopic suprascaoular nerve decompression (tears>3-5cm) <u>Standard surgical repair</u> <ul style="list-style-type: none"> • Double-row sutures or anchors in all 	<ul style="list-style-type: none"> • Bovine BCI attached to bursal side of tendon^d after standard surgical repair 	US
Subpopulations 1 & 2 (mixed)				
ACTRN12611001 082998 Bokor et al. (2015) (1)	9	<ul style="list-style-type: none"> • Arthroscopic (or mini-open) assessment^a • Subacromial bursectomy and decompression <u>Standard surgical repair</u> <ul style="list-style-type: none"> • Take-down repair performed for 1 patient (11%) with high-grade PTRCT • Double-row of suture anchors in 8 (89%) and single-row in 1 (11%) 	<ul style="list-style-type: none"> • Bovine BCI attached to bursal side of tendon^b after standard surgical repair <ul style="list-style-type: none"> • Arthroscopic: 5 (55%) • Mini-open: 4 (45%) 	Australia
Arnoczky et al. 2017 (28)	7	<ul style="list-style-type: none"> • Arthroscopic surgical repair of supraspinatus <u>Standard surgical repair</u> <ul style="list-style-type: none"> • Take-down repair performed for 1 patient (14%) with high-grade PTRCT 	<ul style="list-style-type: none"> • Bovine BCI attached to bursal side of tendon <u>Second procedure: biopsy</u> <ul style="list-style-type: none"> • New tissue generated by bovine BCI 	US

Source: Compiled from Application Form and accessing Thon et al. 2019 (19)

Abbreviations: BCI = bioinductive collagen implant; FTRCT = full-thickness rotator cuff tear; PTRCT = partial-thickness rotator cuff tear; US = United States; int = intermediate;

^a If indicated biceps tendonsis or tenotomy

^b Alignment of implant centred over repaired supraspinatus and laterally positioned to overlap onto bone ~5mm beyond lateral edge of supraspinatus footprint

^c If indicated biceps tendonsis or tenotomy, debridement of minor fraying of the labrum or cuff tendon ,and/or release of the coraco-acromial ligament

^d Alignment of implant centred over repaired supraspinatus and infraspinatus tendons

Comparator

Standard surgical repair (i.e. without use of bovine BCI) is the Applicant's nominated comparator.

Subpopulation 1

The Applicant proposed that use of bovine BCI would be an alternative treatment option to standard surgical repair of symptomatic PTRCTs. *Specifically, it would be provided in addition (i.e. add on service) to debridement and bursectomy, performed as part of standard surgical repair of PTRCTs.*

PASC noted REGENETEN replaces the need for trans-tendon repair and take-down repair (i.e. standard surgical repair) for patients with a PTRCT. However, it does not replace the need for debridement and bursectomy (i.e. REGENETEN is performed in addition to debridement and bursectomy).

The surgical options for symptomatic PTRCTs are non-repair surgery, or debridement⁵ (i.e. smooth the tendon tear), and surgical repair. These procedures may be carried out alone or together, and should always be performed arthroscopically (3). *However, patients with symptomatic PTRCTs typically are expected to require standard repair surgery, using sutures or anchors.*

Specifically, the Applicant stated that standard surgical treatment for PTRCTs has evolved from simple arthroscopic debridement to surgical repair procedures, which there are two techniques:

- Trans-tendon repair; and
- Take-down and repair (7).

The trans-tendon repair involves maintaining the intact lateral portion of the tendon while repairing the medial aspect of the tendon. Following this, standard rotator cuff repair is performed using anchors and sutures. Theoretical benefits of a trans-tendon repair include anatomic restoration of the footprint and maintenance of the normal intact lateral cuff, which may improve biological or biomechanical characteristics and enhance healing (40).

The take-down and repair procedure involves artificially completing the tear during the surgery followed by standard rotator cuff repair using anchors and sutures (40). Although some surgeons advocate this technique, there is a reported failure rate of up to 18% (27). In addition, post-operative care is typically longer with this method (relative to trans-tendon technique) and may include six weeks of shoulder immobilisation (e.g. in sling) and rehabilitation over six months (27).

Specifically, for patients with articular-sided PTRCT, it is suggested both standard surgical repair procedures should be considered when the tear depth > 50% tendon thickness (7) (or Grade III according to Ellman).

The *I.S.Mu.L.T 'Rotator Cuff Tear Guidelines'* state that arthroscopic debridement with or without acromioplasty, and the surgical repair techniques (transtendinous or "completion and repair [i.e. take-down and repair]" technique) are the most frequent treatments for PTRCTs. However, these

⁵ Non-surgical repair or debridement includes several procedures: acromioplasty, subacromial bursectomy, smoothing of tendon lesions, excision of the coraco-acromial ligament, tenotomy or tenodesis of the long head of the biceps brachii, and procedures on the acromioclavicular joint (Beaudreuil 2010) (3)

Guidelines advise that current evidence is low level, which does not allow determination of best treatment (26).

Subpopulation 2

The Applicant proposed that the use of bovine BCI would be in addition (i.e. add-on service) to surgical repair for symptomatic FTRCTs (subpopulation 2) [Application Form, p15], which require the use of standard sutures or anchors.

Standard surgical treatment for symptomatic FTRCTs is performed arthroscopically or as 'mini-open' surgery, and involves reattaching the muscle to the bone using standard sutures or anchors.

Prognostic factors, identified from case-series studies, have indicated the following outcomes following FTRCT surgery:

- Univariate analyses: Higher rate of secondary tearing AND/OR poorer clinical outcomes after repair by arthroscopy or open surgery are associated with the following:
 - Extent of tear (extension to infraspinatus muscle);
 - Tendon retraction;
 - Decrease in pre-operative subacromial height on X-ray;
 - Extensive fatty degeneration (assessed by computed tomography (CT) scan); and
 - Occupation.
- Multivariate analyses: Main negative prognostic factors for direct open repair of FTRCTs are long standing pre-operative signs, poor general health, former or current smoker (>40 pack-years) and a large tear ($\geq 5\text{cm}^2$) found during the procedure. Furthermore a tear of the subscapularis can be a negative prognostic factor for postoperative recovery (3).

Suturing

All rotator cuff tears (arthroscopic or mini-open) are surgically repaired with standard sutures or anchors. There are several techniques:

- Single-row: most common technique but reported high, up to 90% failure rates in case of large and massive injuries; and
- Double-row⁶: more resistant than single-row, but will impart greater strain on repaired tendon (26).

A 2013 meta-analysis of randomised controlled trials showed similar rates of re-tear using single- and double-row suture techniques (41).

Rationale

Simple arthroscopic debridement (with or without subacromial decompression) could be a comparator for some patients with symptomatic PTRCT < 50% tendon thickness (or Ellman Grade II or less), and for patients with symptomatic FTRCTs that are not amenable to direct repair. FTRCTs that are considered not amenable to direct repair are tears that are not reducible without tension or tears with > stage 2 fatty degeneration (3).

Prosthetic surgery (e.g. humeral prosthesis or a total reversed prosthesis) is also an option for a patients with (index) shoulder with co-existing rotator cuff arthropathy (e.g. rotator cuff tear with

⁶ Double-row techniques increase costs in terms of materials and time of the operating room (Olivia 2015) (26)

joint disease, such as arthritis) and pseudo-paralytic symptoms due to a massive rotator cuff tear. However, a prosthesis is only indicated if all other treatment options have been exhausted (3).

Existing MBS items for standard surgical repair

The Applicant stated that standard surgical repair for both populations is currently claimed on the MBS using items 48960, 48906, 48918 and 48909 (Table 7). In addition, MBS items for anaesthesia and surgical assistants may be co-claimed with the items for surgical repair of the rotator cuff.

Table 7: Existing MBS items associated with standard surgical repair of the shoulder

Category 3 –Therapeutic Procedures Subgroup 15 - Orthopaedic
<p>48960 SHOULDER, reconstruction or repair of, including repair of rotator cuff by arthroscopic, arthroscopic assisted or mini open means; arthroscopic acromioplasty; or resection of acromioclavicular joint by separate approach when performed - not being a service associated with any other procedure of the shoulder region Multiple Operation Rule (Anaes.) (Assist.) Fee: \$941.45 Benefit: 75% = \$706.10</p>
Category 3 –Therapeutic Procedures Subgroup 15 - Orthopaedic
<p>48906 SHOULDER, repair of rotator cuff, including excision of coraco-acromial ligament or removal of calcium deposit from cuff, or both - not being a service associated with a service to which item 48900 applies Multiple Operation Rule (Anaes.) (Assist.) Fee: \$564.85 Benefit: 75% = \$423.65</p>
Category 3 –Therapeutic Procedures Subgroup 15 - Orthopaedic
<p>48909 SHOULDER, repair of rotator cuff, including decompression of subacromial space by acromioplasty, excision of coraco-acromial ligament and distal clavicle, or any combination, not being a service associated with a service to which item 48903 applies Multiple Operation Rule (Anaes.) (Assist.) Fee: \$753.25 Benefit: 75% = \$564.95</p>
Category 3 –Therapeutic Procedures Subgroup 15 - Orthopaedic
<p>48918 SHOULDER, total replacement arthroplasty of, including any associated rotator cuff repair Multiple Operation Rule (Anaes.) (Assist.) Fee: \$753.25 Benefit: 75% = \$564.95</p>

Source: MBS online, Medicare Benefits Schedule (42)

It was noted that MBS items 48960 and 48918 are not specific to rotator cuff repair. These items also include shoulder reconstruction, resection and replacement. *In addition, these MBS items do not describe severity of the rotator cuff (partial or full-thickness), do not specify an age criteria or other clinical requirements in respect of prior treatments (e.g. failure of conservative management) that would apply to proposed use of bovine BCI in conjunction with surgical repair of rotator cuff tears.*

MBS utilisation data (over the last four financial years) for the nominated MBS items are provided in Figure 2. The majority (>50%) of MBS use for standard surgical repair is claimed through item 48960.

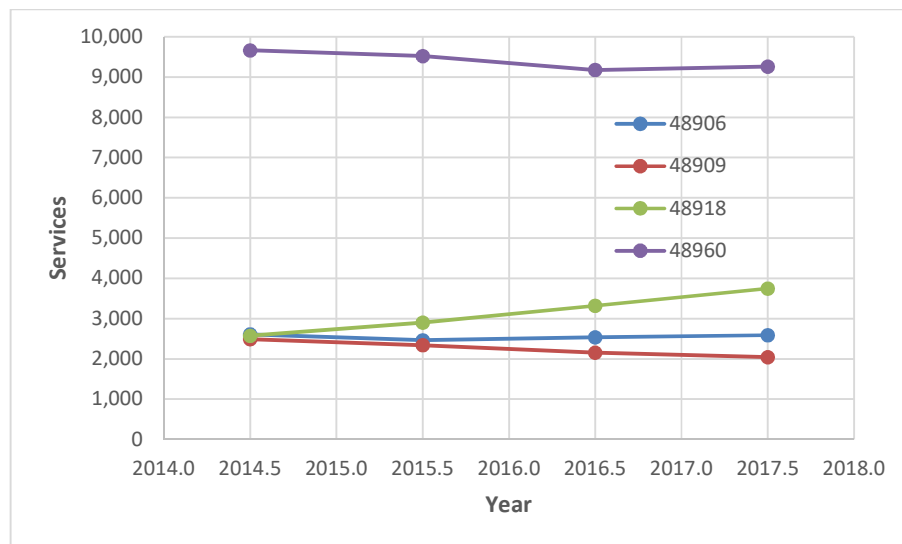


Figure 2: Recent MBS utilisation for nominated items that include standard surgery for rotator cuff repair

Source: Application Form, pp17-18 (verified to be correct accessing http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp (43))

MBS = Medicare Benefits Schedule

Note, Results are provided per financial year (2014.5 = 2014/15 June)

Outcomes

Patient-relevant outcomes

Safety outcomes:

- Procedural complications
- Longer term adverse events
- Revision surgery

Clinical effectiveness outcomes:

PASC nominated additional patient-reported outcomes, assessing shoulder function: Oxford Shoulder Score (OSS) and the Shoulder Pain and Disability Index (SPADI).

Functional outcomes

- American Shoulder and Elbow Surgeons standardized Form for the Assessment of the Shoulder (ASES)⁷
- Constant-Murley shoulder score⁹
- *Oxford Shoulder Score (OSS)*
- *Shoulder Pain and Disability Index (SPADI)*
- Shoulder pain
- Post-operative physical therapy
- Post-operative return to activities

⁷ Note, the ASES and Constant Murley shoulder score are validated shoulder-specific assessments that include both functional parameters and pain assessment.

- Single Assessment Numeric Evaluation (SANE)
- *Progression to full-thickness tear (if subpopulation 1); outcome reported in NCT03734536 (29) (see Table 8 below)*

Imaging-based outcomes

- Tendon thickness
- Size of the cuff defect (tear size, *re-tear rate*)

Quality of life

PASC noted that the EuroQoL-five dimension scale (EQ-5D) and Short Form-36 Health Survey (SF-36) would be appropriate tools to measure health-related quality of life.

- The Applicant did not nominate a specific quality of life instrument, but it was noted the Veterans RAND 12 Item Health Survey⁸ will be administered in the upcoming REDACTED Registry (REDACTED; see Table 8).

For assessment of clinical efficacy of bovine BCI in rotator cuff surgical repair (PTRCTs/FTRCTs), the current peer-review evidence indicates that many patients received other procedures in conjunction with bovine BCI (e.g. ± biceps tenotomy; see Table 6), which could make the treatment effect (e.g. safety, efficacy and quality of life outcomes) of bovine BCI alone difficult to measure. Comparative randomised controlled trial evidence would likely alleviate this concern.

The following additional outcomes were nominated:

Secondary effectiveness outcomes:

- Length of hospital stay
- Time to return to work

[Healthcare system outcomes](#)

The Applicant nominated the following economic outcomes:

Cost-effectiveness

- Resource utilisation (surgical costs, diagnostic test, follow-up physiotherapy rehabilitation, pain management medication, and indirect costs (e.g. work days lost))
- Cost per life year gained, cost per quality-adjusted life year (QALY) gained, and incremental cost-effectiveness ratio.

With the potential availability of bovine BCI funded through the Prostheses List, the following changes in patterns of healthcare resource use may occur (relative to standard surgical repair):

Healthcare system perspective: [specific to each subpopulation]

Subpopulation 1

There would be a potential decrease in hospital (operative) resources required if bovine BCI was applied to patients with symptomatic PTRCTs. The Applicant claimed that, for phase three of the surgical procedure, the use of bovine BCI in the intervention arm would take an average 15-30

⁸ Generic, multi use, self administered health survey comprising of 12 items and items on questionnaire corresponding to eight health domains physical functioning, role limitations due to physical and emotional problems, bodily pain, energy-fatigue, social functioning and mental health

minutes, compared to the comparator arm (without bovine BCI), which has an average surgery time of 30-60 minutes in repair of patients with symptomatic PTRCTs (32).

Subpopulation 2

There would be a potential increase in hospital (operative) resources required if bovine BCI was applied to patients with symptomatic PTRCTs. The Applicant claimed this is due to both the intervention and comparator arms receiving standard arthroscopic or open rotator cuff surgery, using sutures or anchors (phase 3 in this population), and the intervention arm would receive the additional 15-30 minute bovine BCI surgical procedure. This results in surgical time of 45-90 minutes vs. the standard 30-60 minutes for standard surgical repair without bovine BCI (32) (see Table 5).

Healthcare system perspective: [both subpopulations]

- A potential decrease in resources (hospital- and/or community-based services) required for the post-operative management and rehabilitation of patients treated with bovine BCI procedure. Based on expert opinion, the Applicant advised that patients who receive surgery with bovine BCI may only need one week in a sling, with six weeks rehabilitation, compared with 6 weeks in a sling and between 6-9 months recovery with standard surgical repair [Application Form, p15]. The Applicant-nominated clinical expert advised that many patients do not willingly choose conventional surgery, as it involves a lengthy recovery period, during which their activities are restricted. Specifically, resources that could decrease within rehabilitation programs include diagnostic testing (e.g. MRI is performed as standard practice 6 months post-operative if patients have not improved); allied health services (e.g. physiotherapy); and services and/or treatments for pain management (e.g. NSAIDs and/or corticosteroid injections).
- A potential decrease in hospital resources (operative) if the use of bovine BCI results in fewer patients requiring subsequent surgical revision, due to clinical failure of the primary rotator cuff tear procedure. Schlegel et al., (2018) (27) reported that none of the patients with symptomatic PTRCTs repaired using BCI (who followed the post-operative rehabilitation protocol) needed any revision surgery through to 1-year follow-up. Similarly, Bokor et al. (1, 2) reported no tear progression or re-tears were observed during 24-month follow-up. However, in a population with advanced PTRCT disease (large and massive tears), two patients (9%) had clinical failure, with one requiring revision surgery with reverse shoulder arthroplasty, due to progression of the patient's arthritis and further atrophy of rotator cuff (Thon et al 2019 (19)) (see efficacy results for bovine BCI in Table 9).

Societal perspective: [both subpopulations]

- A potential increase in productivity gains through patients returning more quickly to usual daily activities, including work.

Financial implications

The following outcomes were nominated:

Total Australian Government healthcare costs

- Total cost to Medicare Benefits Schedule and Australian Government budgets.

Rationale

The outcomes assessed (in the current evidence base and upcoming studies) are summarised in Table 8. *It was noted the current evidence base assessing efficacy and safety of bovine BCI in surgical repair of rotator cuff tears in Australia is from early feasibility studies, providing up to 2 years of follow-up, albeit in small (n<30) patient numbers.*

Table 8: Summary of outcomes assessed in current (and upcoming) evidence base for bovine BCI in rotator cuff surgical repair

Study ID	N	Primary outcome	Secondary outcome	Country (duration)
PEER REVIEW				
Subpopulation 1 (PTRCT)				
ACTRN12611001082998 Bokor et al. (2016) (2)	13	<ul style="list-style-type: none"> Imaging-based outcomes (MRI): tendon thickness, defect size & tendon quality 	<ul style="list-style-type: none"> Clinical outcomes: ASES, Constant Murley shoulder score Quality of life: SF-36: NR in publication* 	Australia (2 years)
Schlegel et al 2018 (27) (REDACTED)	33	<ul style="list-style-type: none"> Imaging-based outcomes (MRI): tendon thickness, defect size & tendon quality 	<ul style="list-style-type: none"> Clinical outcomes: ASES, Constant Murley shoulder score 	US (1 year)
Subpopulation 2 (FTRCT)				
Thon et al. 2019 (19)	23	<ul style="list-style-type: none"> Safety with implant use, AEs^a Clinical failure^b 	<ul style="list-style-type: none"> Imaging-based outcomes (US and MRI): tendon thickness, tendon continuity ASES (final follow-up) Secondary treatment failure^c 	US (2 years)
Subpopulations 1 & 2 (mixed)				
ACTRN12611001082998 Bokor et al. (2015) (1)	9	<ul style="list-style-type: none"> Imaging-based outcomes (MRI): tendon thickness, defect size & tendon quality 	<ul style="list-style-type: none"> Clinical outcomes: ASES, Constant Murley shoulder score Quality of life: SF-36: NR in publication* 	Australia (1 year)
Arnoczky 2017 (28)	7	<ul style="list-style-type: none"> Biopsy outcomes 		US (≤ 20 months)
YET TO BE COMPLETED				
Subpopulation 1 (PTRCT)				
REGEN PUB 2018 REDACTED	118	<ul style="list-style-type: none"> ASES score tear using standard techniques (3 months) 	<ul style="list-style-type: none"> ASES score, ASES VAS score SANE score Shoulder stiffness VAS score Cumulative opioid use Duration of shoulder immobilization Progression to FTCRT Incidence of revision surgery Aggregate health care utilization costs Operating room time Number of steroid injections Number of unscheduled clinic visits and on-cause imaging 	US (2 years)
Subpopulations 1 & 2 (mixed)				
Registry REDACTED	483 ^d	<ul style="list-style-type: none"> Shoulder pain, Δ VAS ASES SANE 	<ul style="list-style-type: none"> Safety: AEs and SAEs Recovery: cumulative days in sling, days between discharge- and return 	US (1 year)

Study ID	N	Primary outcome	Secondary outcome	Country (duration)
		<ul style="list-style-type: none"> •VR-12 •WORC 	to work –return to driving –overhead throwing –non overhead sport, cumulative physical therapy, cumulative narcotic medication, cumulative injections and revision surgery	
Post-market evaluation REDACTED	148	<ul style="list-style-type: none"> •Increase in tendon thickness •Integration of new tissue •Fill in of PTRCT and tendon quality •Re-tear rate (assessed by MRI) 	<ul style="list-style-type: none"> •Safety: AEs •Procedural parameters •ASES •Constant Murley shoulder score •Postoperative recovery time •Subject satisfaction 	US (1 year)

Source: Compiled during development of the PICO, from publications listed above and Clinicaltrials.gov

Abbreviations: AE= adverse event; ASES = American Shoulder and Elbow Surgeons; MRI = magnetic resonance imaging; NR = not reported; SAE = serious adverse event; SANE = Single Assessment Numeric Value; SF-36 = Short Form 36 health survey; US = ultrasound; VAS = visual analogue scale; VR-12 = Veterans RAND 12 Item Health Survey; WORC = Western Ontario Rotator Cuff Index; US = United States; Δ = change (incremental)

^a Included but not limited to hospitalisation, medical or surgical intervention, further illness, worsening or permanent impairment, implant loosening, allergic reaction, or death

^b Failure determined as any implant-related adverse event, any failure of the implant itself, noted complications attributed to the implant, or any implant-related tissue reaction during the study period

^c Lack of healing on either imaging modality (US and MRI) or the need for additional surgical procedures to be performed on the same shoulder during the study period, including conversion to reverse total shoulder arthroplasty

^d Listed as enrolled on Clinicaltrials.gov; REDACTED

*The Applicant advised from feedback from the primary author indicated that the results from SF-36 did not show anything unexpected as all patients showed improvement following receipt of REGENETEN™ and there was not anything unremarkable to report on(32)

Current and proposed clinical management algorithm for identified population

The Applicant’s current and proposed clinical management algorithm was based on consultation with experts [Application Form, p11], as there are currently no Australian specific guidelines for repair of rotator cuff tears. Specifically, there is no consensus on a single algorithmic treatment approach to patients with a symptomatic PTRCT (2). *The place of bovine BCI, performed in addition to arthroscopic surgery (debridement and bursectomy) in **subpopulation 1**, and in addition to standard arthroscopic or min-open surgical repair in **subpopulation 2**, was highlighted in red during preparation of the PICO (see Figure 3 below). In addition, downstream options were also added during preparation of the PICO. The current and proposed clinical management algorithm for the identified population is provided in Figure 3 below.*

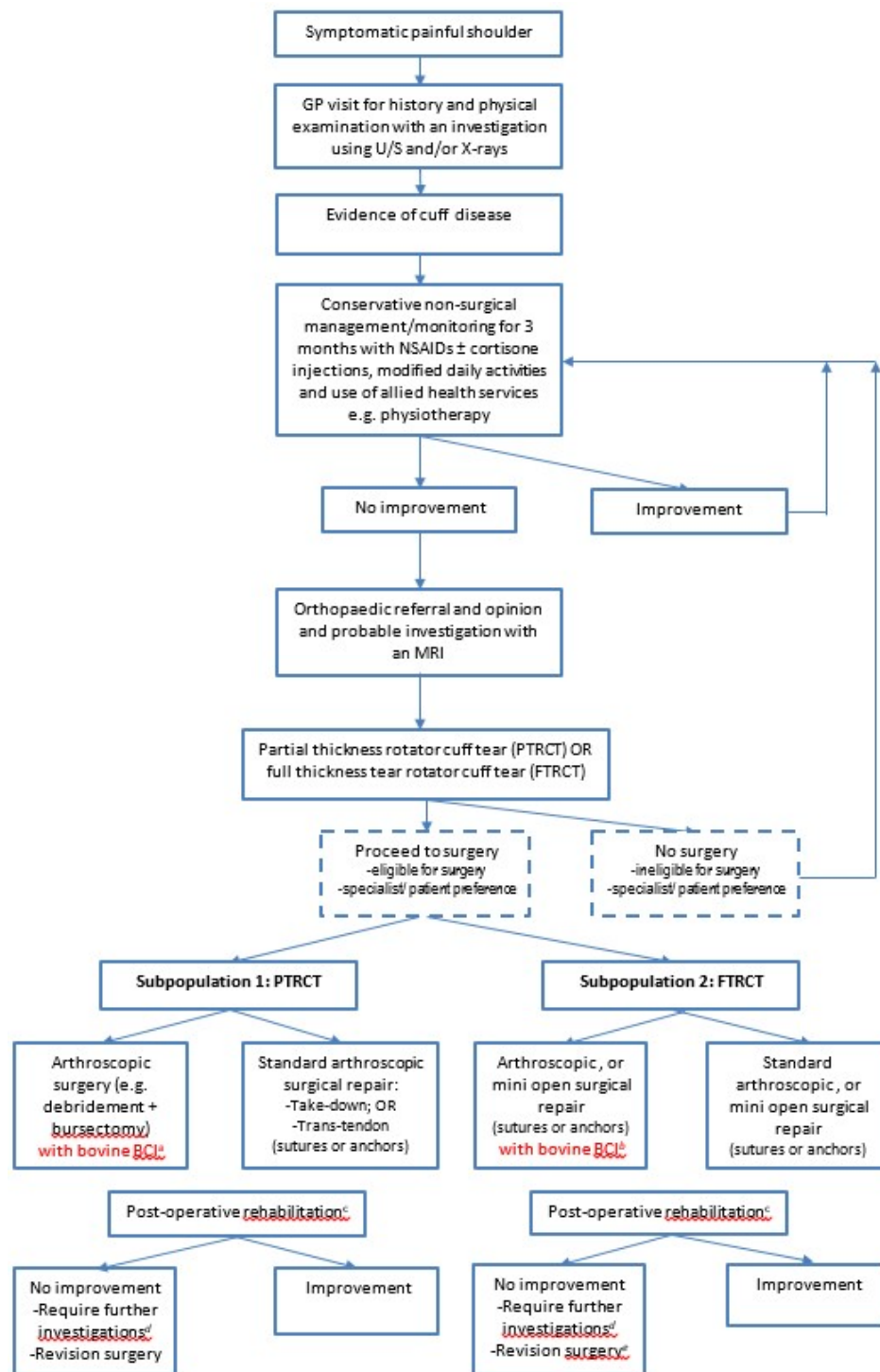


Figure 3: Current and proposed algorithm for subpopulation 1 (PTRCT) and subpopulation 2 (FTRCT)

Source: Compiled from Appendix A [Application Form, p21]

Abbreviations: BCI = bioinductive collagen implant MRI = magnetic resonance imaging; MRA = magnetic resonance arthrography; NSAID = nonsteroidal anti-inflammatory drugs; U/S = ultrasound

^a 1 patient with a high-grade PTRCT received bovine BCI following a take-down repair (sutures or anchors) in Bokor 2015 (1)

^b All patients with FTRCTs in Bokor et al 2015 (1) and Thon et al. 2019 (19) received bovine BCI after surgical repair (sutures or anchors)

^c Applicant stated that after receiving surgery patients are followed up for 3 months as routine practice [Application Form, p15]

^d Possible investigations could include imaging (MRI), physical therapy sessions, and treatments for pain management

^e 2 patients with FTRCTs (large or massive) had clinical failure in Thon et al. 2019 (19), resulting in 1 requiring revision surgery with reverse shoulder arthroplasty, due to progression of arthritis

A key difference between the intervention and comparator in **subpopulation 1** is that bovine BCI can be used without standard repair techniques, using sutures or anchors.

The Applicant stated that after receiving surgery, patients are followed up for 3 months, as routine practice. Downstream services such as post-operative rehabilitation includes services associated with diagnostic imaging (X-ray and/or ultrasound and/or MRI), physical therapy sessions from physiotherapists and treatments for pain management (NSAIDs ± corticosteroid injections).

PASC noted that the usual care for patients with a PTRCT is MRI (at diagnosis) and follow-up MRI, regardless of tear status. PASC considered this to be important when considering resources.

The Applicant stated that following standard surgical repair (in either subpopulation), a repeat procedure (e.g. revision surgery) may be performed under the discretion of the surgeon if the repair was considered to have failed [Application Form, p15].

It was noted that following surgical repair with bovine BCI failure in Thon et al. 2019 (19), failure was defined as “any implant-related adverse event, any failure of the implant itself, noted complications attributed to the implant, or any implant-related tissue reaction during the study period”. Secondary treatment failure was a lack of healing on either imaging modality (ultrasound and/or MRI) or the need for additional surgical procedures to be performed on the same shoulder during the study period, including conversion to reverse total shoulder arthroplasty.

PASC queried the possibility of repeat procedures. The Applicant advised this is unlikely, as REGENETEN is unlikely to succeed on a second attempt, if it has already failed.

PASC queried the steps to be taken if REGENETEN fails on the first attempt. The Applicant stated that conventional surgery may be an option, if the clinician and patient choose and agree on that route.

PASC considered REGENETEN to be a ‘once-only’ procedure per tendon.

Proposed economic evaluation

The evidence reporting efficacy and safety outcomes of bovine BCI use in rotator cuff surgical repair is currently represented by prospective single-arm studies and retrospective cohort studies (e.g. level IV evidence⁹; see Table 9 below). Thus, assessment of the comparative effectiveness and safety of bovine BCI in surgical repair of rotator cuff tears vs. standard surgical repair of rotator cuff tears (without use of bovine BCI) is likely to be based on an indirect or naïve comparison of outcomes.

However, it was noted REGEN PUB 2018 (REDACTED) (29) could provide comparative evidence by including standard surgical repair (without use of bovine BCI) in symptomatic PTRCTs (**subpopulation 1**), in one treatment arm of the study.

Table 9: Summary of current clinical evidence for surgical repair with bovine BCI (REGENETEN)

Study ID	N	Study type	Key outcomes results	Country
PEER REVIEW				
Subpopulation 1 (PTRCT)				
ACTRN12611001082998 Bokor et al. (2016) (2)	13	Prospective, OL, NR, single arm, SC Level IV ^a	<ul style="list-style-type: none"> • Significantly improved clinical scores (Constant-Murley and ASES; p=0.001) • Significant new tissue formation (p<0.0001) 	Australia

⁹ By National Health and Medical Research Council (NHMRC) levels of evidence

Study ID	N	Study type	Key outcomes results	Country
			<ul style="list-style-type: none"> • No tear progression at 24 months 	
Schlegel et al 2018 (27) REDACTED	33	Prospective, OL, NR, single arm, MC Level IV ^a	<ul style="list-style-type: none"> • Significantly improved clinical scores (Constant-Murley and ASES; p<0.001) • Mean tendon thickness increased by 2.0mm (p<0.0001) • No serious adverse events related to implant 	US
Subpopulation 2 (FTRCT)				
Thon et al. 2019 (19)	23	Prospective, OL, NR, single arm, MC Level IV ^a	<ul style="list-style-type: none"> • No adverse events attributed to implant • Clinical failure^c = 2 patients (9%), 1 requiring additional surgery arthroplasty, due to progression of pain and dysfunction • MRI rotator cuff thickness = 5.13 ±1.06mm • Mean ASES at final follow-up = 82.87 ±16.68 	US
Subpopulations 1 & 2 (mixed)				
ACTRN12611001082998 Bokor et al. (2015) (1)	9	Prospective, OL, NR, single arm, SC Level IV ^a	<ul style="list-style-type: none"> • Significantly improved clinical scores (Constant-Murley and ASES; p<0.01) • Significant mean tendon thickness increased (p<0.01) • No re-tears observed during 24-month follow-up 	Australia
Arnoczky 2017 (28)	7	Retro, OL, NR, single arm, SC Level IV ^a	<u>Biopsy related outcomes:</u> <ul style="list-style-type: none"> • Increased collagen formation, maturation and organisation • Newly generated tissue at 6 month^b 	US

Source: pp6-7 of Application Form and Thon et al. 2019 (19)

Abbreviations: ASES = American Shoulder and Elbow Surgeons; FTRCT = full-thickness rotator cuff tear; MC = multi-centre; MRI = magnetic resonance imaging; NR = non randomised; OL = open label; PTRCT = partial-thickness rotator cuff tear; Retro = retrospective; RA = rheumatoid arthritis; SC = single-centre; US = United States; int = intermediate; med = medium

^a National Health and Medical Research Council (NHMRC) levels of evidence

^b Implant generated host tissue rapidly matured into tendon tissue

^c Was defined as lack of healing on either imaging modality (US and/or MRI) or the need for additional surgical procedures to be performed on the same shoulder during the study period, including conversion to reverse total shoulder arthroplasty.

For both patient subpopulations, the Applicant advised that the comparative clinical claim is likely to be superior effectiveness for functional outcomes and similar safety. Therefore, a cost-effectiveness analysis or cost-utility analysis would be appropriate.

It was noted that no economic evaluations assessing use of bovine BCI in surgical repair of rotator cuff tears vs. standard surgical repair (without use of bovine BCI) were provided in the Application Form, or located during the rapid review of the literature.

Proposed MBS item descriptor

This Application (MSAC 1593) is linked to a co-dependent PLAC application for listing bovine BCI (used in surgical repair of rotator cuff tears) on the Prostheses List (with the prosthesis to be used in conjunction with existing MBS items). No new MBS item was requested by the Applicant.

The Applicant provided the breakdown of estimated procedure costs associated with arthroscopic implantation of bovine BCI for the treatment of rotator cuff repair (Table 10).

Table 10: Cost of bovine BCI, applied arthroscopically, in surgical repair of rotator cuff tears

Row	Component	Cost/ MBS fee	Cost/MBS hospital rebate	Source/calculation
A	Prostheses List benefit (through PHI): BCI	REDACTED	REDACTED	Applicant
B	Pre-anaesthesia consultation	\$43.65	75%: \$32.75	MBS item 17610
C	Initiation anaesthesia	\$99.00	75%:\$74.25	MBS item 21622

Row	Component	Cost/ MBS fee	Cost/MBS hospital rebate	Source/calculation
D	Arthroscopic (or mini-open) ^a surgery including application of BCI	\$941.45	75%: \$706.10	MBS item 48960
E	Anaesthesia (26-30 minutes) ^b required for application of bovine BCI in subpopulation 1 (phase 3) and subpopulation 2 (phase 4)	\$39.60	75%: 29.70	MBS item 23023
F	Total	REDACTED	REDACTED	Sum (A:E)

Source: p20 of Application Form

Abbreviations: BCI = bioinductive collagen implant; MBS = Medicare Benefits Schedule;

^a This approach is also included in MBS item 48960 (i.e. same MBS fee/rebate for arthroscopic or mini-open technique)

^b Applicant advised that the estimated time of the procedure is 15-30 minutes

The Applicant advised that use of bovine BCI would be claimed on the MBS using items that relate to surgical repair of rotator cuff tears. The Applicant specified three MBS item descriptors (MBS items 48960, 48906 and 48909; see Table 7) that would apply to the proposed intervention.

PASC confirmed MBS items 48960, 48906 and 48909 are suitable for this procedure, and noted item 48960 is the most applicable item (given it refers to arthroscopic repair).

PASC noted these three items cannot be co-claimed.

Although ‘mini-open’ and arthroscopic rotator cuff surgical repair techniques attract the same MBS fee (included in MBS item 48960), the *I.S.Mu.L.T Guidelines* indicate that arthroscopy is more expensive and requires more operative time than the ‘mini-open’ technique (26). *In the assessment phase, if data was available for operating room time in patients treated with arthroscopic vs. mini-open techniques in subpopulation 2, this could be incorporated in the assessment of cost-effectiveness (however, noting this inclusion is not critical as it would not be expected to be driving incremental differences in assessment of cost-effectiveness).*

Consultation feedback

PASC noted the support for Application 1593 from the Shoulder and Elbow Society of Australia (specifically in the Society’s ‘Statement of Clinical Relevance’).

Next step

Following ratification of PICO 1593, this application PROCEEDED to the pre-Evaluation Sub-Committee (ESC) stage, with the Applicant nominating to prepare its own ADAR (Applicant-developed assessment report).

Appendix

Population

Table 11: Rotator cuff tendon dimensions

Rotator cuff tendon	Medial to lateral Mean (mm)	width Range (mm)	Anterior to posterior Mean (mm)	width Range (mm)
Supraspinatus	16	12-20	23	18-33
Infraspinatus	18	12-24	28	20-45
Teres minor	21	10-33	29	20-40
Subscapularis	20	15-25	40	35-55

Source: Table 1 of Matthewson 2015 (5)

Table 12: Classification of PTRCTs: articular, bursal and intratendinous locations

Grade	Size of tear	Percentage of tendon thickness
I	<3mm	<25%
II ^a	3-6mm ^a	25-50%
III ^b	>6mm ^b	>50% (but less than full-thickness)

Source: Table 2 of Matthewson 2015 (5)

Abbreviations: PTRCT = partial-thickness rotator cuff tear

^a Classified as intermediate in Bokor 2016 (2)

^b Classified as high in Bokor 2016 (2)

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